REMARKS

Status of the Claims

Following this Amendment, Claims 40-72 and 74-91 are now pending in the application. In the present Amendment, Claim 73 has been canceled, Claims 40-42, 53-60, 62-72, and 74-75 have been amended and new claims 77-91 have been added. Support for these new and amended claims can be found throughout the specification and the originally filed claims. Applicants have not introduced any new matter by the amendments.

Specifically, support for culturing a bacterium or yeast can be found at page 14, line 30 to page 15, line 9. Support for bacterial and yeast glucosamine-6-phosphate synthases can be found at page 15, line 10 to page 17, line 5. Support for the partial or complete deletion of a gene encoding a protein recited in Claim 80 can be found, *inter alia*, in Example 1.

Claim Objections

Claim 73 was objected to under 37 C.F.R. § 1.75 as being the substantial duplicate of claim 50. Claim 73 has been canceled. Accordingly, Applicants respectfully request that this objection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 40-76 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for directly or indirectly reciting the phrase "increased glucosamine-6-phosphate synthase activity." Claims 40, 55-60, 65, 67-70 and 72 have been amended to clarify that the increase or decrease in enzymatic activity is in relation to the unmodified enzyme, as suggested by the Examiner. Claims 41-54, 61-64, 66 and 74-76

depend from the amended claims and thus also contain the clarified language. Independent Claim 71 does not recite the phrase and thus does not require amendment. Claim 73 has been canceled.

Accordingly, in light of the amendments discussed above, Applicants respectfully request that all rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Enablement

Claims 40-76 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. According to the Office, the specification does not provide guidance regarding the specific type of genetic modification to perform on the specific codons within the coding region of any polynucleotide encoding glucosamine-6-phosphate synthase. Office Action, page 4. Applicants traverse this rejection.

Applicants respectfully remind the Examiner that the present claims do not recite specific sequences of glucosamine-6-phosphate synthases, i.e., sequences with specific amino acid mutations. Rather, the amended claims recite a bacterium or yeast that comprises at least one genetic modification that increases the activity of glucosamine-6-phosphate synthase compared to the unmodified glucosamine-6-phosphate synthase.

To satisfy the enablement requirement, the specification must contain sufficient disclosure to enable one skilled in the art to make and use the claimed invention without undue experimentation. M.P.E.P. § 2164. A determination of whether the claims are enabled thus involves, *inter alia*, the level of skill in the art and the amount of direction

provided by the inventor. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants submit that the specification provides sufficient disclosure to allow one of skill in the art to practice the full scope of the claims.

The present specification specifically exemplifies the making of bacteria that express a recombinant nucleic acid molecule encoding a bacterial or yeast glucosamine-6-phosphate synthase. The inventors also disclose the production of at least three bacterial strains that express a recombinant nucleic acid molecule encoding a bacterial or yeast glucosamine-6-phosphate synthase, wherein said synthase has glucosamine-6-phosphate synthase enzymatic activity and comprises a genetic modification that reduces the glucosamine-6-phosphate product inhibition of said glucosamine-6-phosphate synthase (which results in increased glucosamine-6-phosphate synthase activity) compared to the unmodified glucosamine-6-phosphate synthase.

The specification further discloses that the invention, while exemplified in bacteria, can be applied to other microorganisms that contain similar amino sugar metabolic pathways and genes and proteins having similar structure and function within such pathways. The amino sugar metabolic pathways and genes and proteins involved therein are known in the art for many bacteria and yeast. Indeed, the Examiner has recognized that bacterial or yeast glucosamine-6-phosphate synthases can be used in the claimed methods. Thus, Applicants submit that the specification provides enabling support for the amended claims.

Applicants reiterate the previous arguments concerning the amount of experimentation involved to make and use the bacterial or yeast glucosamine-6-

phosphate synthases with the recited genetic modifications. The present inventors have exemplified the production of bacteria expressing these glucosamine-6-phosphate synthases. The Examiner refers to Guo et al. and presents an argument that:

> "Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for an *E.coli* glucosamine-6-phosphate synthase having 25 mutations (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish...."

However, Applicants submit that this argument is completely contrary to what has been clearly exemplified and described in the present specification and in subsequent declarations and arguments, and further, goes beyond what is actually required by the present claims. In fact, the inventors have demonstrated that in one routine experiment using the methods of the instant claims, not one, not ten, but **96** microorganisms out of 4368 microorganisms (hardly the "few" within "several hundred thousand" proposed by the Examiner) were identified as producers of excess glucosamine compared to the parent strain (see, e.g., Example 5). There is no requirement by the claims to provide a mutated synthase having 25 or 50 mutations; rather, the claims only require that the synthase contain a modification sufficient to increase the synthase activity as compared to the unmodified synthase. Applicants have demonstrated that using current techniques in the art (i.e., high throughput mutagenesis and screening techniques), this result is readily achievable and *did not require an enormous quantity of experimentation, nor take a very long time to accomplish*. Applicants submit that these

teachings provide sufficient guidance to carry out the methods recited in the instant claims without undue experimentation.

Moreover, the specification makes clear that it is not necessary to know where to modify the sequence in order to produce the recited microorganisms and use them in the claimed invention. However, if one wishes to determine the identity of the mutation after the microorganism is identified, this may be accomplished by routine sequencing. The Examiner continues to argue that it is necessary to know what domains and motifs within the amino acid sequence of the *E. coli* glucosamine-6-phosphate synthase can be modified to make a synthase with increased activity. However, the specification, the Declaration of Dr. Deng, and the Declaration of Dr. Demain have provided substantial evidence that this is simply not an accurate statement. The Examiner has not provided a specific rebuttal of these arguments or evidence provided by Applicants, particularly with respect to the Declaration of Dr. Demain, which included significant evidence that knowledge of the specific domains and motifs within a sequence are not necessary to routinely make and use genetically modified microorganisms as claimed. The Examiner has not provided clear and convincing proof that undue experimentation would be required to make and use the invention in view of the substantial evidence presented to the contrary.

Finally, Applicants note that Claim 71 and new Claims 78-79 do not recite the genetic modification language that forms the basis for the enablement rejection. Applicants thus request that the rejection be withdrawn for at least these claims.

Combining the teachings of the specification with the knowledge in the art at the priority date of the application, one of skill in the art could readily make and use the full

scope of the claimed invention without undue experimentation. Therefore, the enablement requirement of 35 U.S.C. § 112, first paragraph, has been satisfied. Applicants thus respectfully request that these rejections by withdrawn.

Written Description

Claims 40-76 were also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the Office, these claims encompass, but the specification does not support, (1) many microorganisms, (2) many glucosamine-6-phosphate synthases from any biological source, and (3) many genetic modifications. Office Action, page 4.

Applicants respectfully traverse these rejections for the reasons of record. However, in an effort to expedite prosecution, Applicants have amended the claims and submit that the specification provides adequate support for the claims as amended. The specification provides specific disclosure and examples of the culturing of bacteria or yeast, as recited in the claims. Likewise, the specification exemplifies bacteria that express nucleic acids encoding bacterial glucosamine-6-phosphate synthases and teaches that the invention may be applied to other microorganisms that contain similar amino sugar metabolic pathways and genes and proteins having similar structure and function within such pathways.

The written description requirement is satisfied if the specification discloses the invention in sufficient detail to allow a person skilled in the art to reasonably conclude that the inventor had possession of the invention as claimed. M.P.E.P. § 2163. While claims drawn to a genus may be adequately supported by the disclosure of a representative number of species within the genus, the Federal Circuit has made clear

that the specification need not describe every permutation of an invention nor subject matter known to those of skill in the art. *Capon v. Eshhar,* 418 F.3d 1349,1359-60 (Fed. Cir. 2005).

As discussed above, the specification exemplifies the invention using bacteria as a model organism but teaches that the invention is applicable to other microorganisms that contain similar amino sugar metabolic pathways and genes and proteins having similar structure and function within such pathways. These pathways, genes and proteins in bacteria and yeast are well known to one of skill in the art. Applicants are not required to list every strain of bacteria or yeast, nor to specifically exemplify every glucosamine-6-phosphate synthase suitable for use in the present invention, since these sequences were already known in the art. As previously argued, the Federal Circuit has made it clear that it is not correct to conclude that "§112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of the claimed DNA, when that sequence is already known in the field". *Capon*, 418 F.3d at 1360-61 (Fed. Cir. 2005); *see also* M.P.E.P. § 2163, page 2100-172 (Rev. 5, Aug. 2006).

The Examiner also asserts that "simply stating that common catalytic amino acids are present is insufficient to provide guidance as to where genetic modifications can be made to increase enzyme activity." Office Action, page 5. However, as set forth previously, Applicants have not merely made such statements, but rather, provided *evidence* that at the time of the invention, the skilled artisan already knew the structural features of glucosamine-6-phosphate synthase that were correlated with function. Again, Fernandez-Herrero et al. (1995, *Mol. Microbiol.* **17(1)**:1-12), one of a few such references provided with prior responses, compares the sequences of glucosamine-6-

phosphate synthases of *E. coli*, *Rhizobium leguminosarum*, *Rhizobium meliloti*, *Thermus thermophilus*, yeast, human and mouse, a set of very divergent species, and specifically shows that all of the enzymes contain key amino acid residues that are mechanistically important for catalytic activity. Therefore, Applicants have provided documentary evidence showing the knowledge in the art at the time of the invention. The Examiner's statements are therefore completely contradictory to what the references show, yet the Examiner has still failed to provide any evidence to support his position.

Referring to the Declaration of Dr. Deng, and the Examiner's statements regarding low homology among different synthases, the fact that synthases with low overall homology to one another still operate in the method of the present invention simply demonstrates that there is great flexibility in the choice of a glucosamine-6-phosphate synthase that can be used in the claimed method. It is clear that given the description in the specification and the knowledge at the time of the invention, the skilled artisan would be able to predict the structure of other species encompassed by the claimed genus by the single description of the *E. coli* glucosamine-6-phosphate synthase. Indeed, the skilled artisan need not *predict* the structure of other species, as many other species of glucosamine-6-phosphate synthase were known at the time of the invention, as evidenced by Applicants.

As explained with regard to the enablement rejection above, the specification provides methods for making and using bacteria or yeast that express bacterial or yeast glucosamine-6-phosphate synthases that comprise the genetic modifications recited in

the claims. The specification also specifically exemplifies the production of many strains of bacteria that comprise these genetic modifications.

Applicants respectfully submit that the specification, in combination with the knowledge in the art, provides adequate support for a bacterium or yeast that expresses a bacterial or yeast glucosamine-6-phosphate synthase comprising the genetic modifications recited in the amended claims.

Therefore, in view of the amendments and explanations provided above, Applicants respectfully submit that the specification provides adequate written description support for all pending claims. Accordingly, Applicants request that all rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner has any questions regarding this Amendment and Response, the Examiner is invited to contact the undersigned at 303-863-9700.

The required three-month extension of time fee of $1020.00 is submitted herewith via EFS-Web. In the event that additional fees are due in connection with this response, please debit Deposit Account No. 19-1970.

Respectfully submitted,

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Dated: February 13, 2007

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